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08/17/94

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1, 3, 5-10, 13, 17-19, 23-24, 28-32, 35, 37-42, 67-76 are pending in the application.
   Of the above, claims 67-76 are withdrawn from consideration.
2. ☒ Claims 2, 4, 11-12, 16, 20-22, 25-27, 33, 34, 36, 43-66 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42, ~~43~~ 67-76 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received
    ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. Claims 2, 4, 11-14, 16, 20-22, 25-27, 33, 34, 36, 43-66 and 77 have been cancelled in response to applicant's amendment.

16. Claims 1, 7-10, 17-19, 23, 24, 28-32, 35 and 37-42 have been amended.

17. Claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42, 67-76 and 78 are pending.

18. Claim 78 has been added.

19. Claims 67-76 have been withdrawn as directed to a non-elected invention.

20. Claim 16 was amended. Applicant is reminded that claim 16 was cancelled in Paper No. 11, dated August 28, 1992. Further, claim 15 was amended to anti-CD2 in Paper No. 17, dated December 16, 1993. This amendment resulted from a rejection to claim 15 on page 3, paragraph 25 of the Office Action dated July 12, 1993 entered as Paper No. 16. The claim has no antecedent basis and was not considered. Additionally, claims 23, 24 and 28-32 depend from cancelled claim 21. This claim was cancelled in the same preliminary amendment that claims 23, 24 and 28-32 were amended, [amendment C_A Paper No. 26, filed May 5, 1994]. Subsequently, these claims have not been considered.

21. Constructively elected claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42 and 78 are under consideration.

22. 35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

23. Claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42 and 78 are rejected under 35 U.S.C. § 101 because the invention as disclosed is inoperative and therefore lacks utility. There is no evidence presented which clearly and reproducible illustrates that there is any utility for the claimed invention. There is no suggestion that any of the disclosed utilities are attainable or even practical.

A) For example concerning the therapeutic or diagnostic utilities of antibodies, Waldmann [Science 252:1657-1662 (1991)] teaches that effective therapy using monoclonal antibodies has been elusive and describes limitations of murine antibodies in the therapy of human diseases due to the pharmacokinetic properties of rodent antibodies in human and human anti-mouse

22.

antibody responses. Waldmann also indicates that hopes for antibody-based treatment methods engendered by in-vitro and animal model studies have not correlated well with in-vivo clinical trail results in patients. Further Harris et al. [TIBTECH 11:42-46 (1993)] state "there is widespread acceptance that there is little future for the use of rodent mAbs for in vivo human therapy", see page 42, column 2, lines 3-7. Harris et al. also teach "the residual HAMA response to chimeric antibodies is mainly anti-idiotypic, therefore repeated dosing is ineffective", see page 42, column 3, lines 17-20. Applicant has only provide evidence of therapeutic use in nude mice, which are immunosuppressed. Nude mice therefore are not a sufficient model system to test anti-murine responses to antibodies. It is well known in the art that antibody-based therapies have very limited success. One of ordinary skill in the art would not readily accept that Applicant's claimed modified antibodies would be satisfactory for human therapy as asserted in the specification. As evidenced by Osband et al. [Immunotherapy 11(6):193-195 (1990)] one of ordinary skill in the art would not readily accept the utility of an immunotherapeutic agent without convincing objective evidence of efficacy in humans (see paragraph bridging pages 193-194). As further evidenced by Waldmann and Dillman [Ann. Internal Med. 111:592-603 (1989)] it is well known in the art that the use of monoclonal antibodies has, in general, only met with very limited success in humans. Waldmann teaches that immunotoxins have not lived up to expectations and that "the results of in vivo clinical trials in patients with cancer with first-generation immunotoxins did not fulfill the hopes engendered by in vitro and animal model studies" (see page 1660, second column, fourth full paragraph). Dillman teaches that "as a therapeutic modality, monoclonal antibodies are still promising but their general use will be delayed for several years" (see Abstract). In addition, Hird et al. [Genes and Cancer (1990) chapter 17] teaches that "the data obtained from mouse studies are useful, but cannot be directly translated to apply to the human situation" (see page 185, first full paragraph). Other factors such as proteolytic degradation, immunological inactivation, antigenic modulation or antigen shedding by the tumor, as well as factors influencing localization of the antibody such as the anatomical location of the tumor and its vascularity and blood flow, all have bearing on the efficacy of the antibody therapy. Further, with respect to immunotoxins, the level of antigen expression and the rate and route of internalization also effect the therapeutic efficacy of the antibody. Given the teachings of Osband et al., Waldmann, Dillman, Hird et al. and Harris et al. as well as the other well known factors effecting antibody therapies, one of ordinary skill in the art would not readily accept Applicant's claimed utility on its face, absent some showing of convincing objective evidence of therapeutic or diagnostic utility. Therefore, the claims are

rejected as lacking patentable utility.

B) Pharmaceutical therapies are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half life of the protein; (2) the protein may otherwise not reach the target area because, for example, (a) the protein may not be able to cross the mucosa, (b) the protein may be adsorbed or absorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo use, i.e. may produce adverse side effects prohibitive to the use of such treatment. See MPEP 608.01(p).

24. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

25. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and for failing to adequately teach how to make and/or use the invention, i.e. for failing to provide an enabling disclosure.

A) Applicant has not disclosed to one of ordinary skill in the art how to use the claimed invention. There is an insufficient written description of the invention with respect to the in-vivo operability of the antibody to enable one of ordinary skill in the art to use applicant's invention, for the reasons discussed in detail in the previous rejection made under 35 U.S.C. § 101. It would require undue experimentation for the skilled artisan to practice applicant's claimed invention from what has been disclosed. As stated above there is a high degree of unpredictability associated with methods such as those claimed.

B) The disclosure does not provide a sufficient enabling description to use the claimed invention in vivo, for the reasons given above.

C) The disclosure provides only a description of B7 antigen on CHO cells. Other immobilized B7 sources have not been enabled by the specification for applicant's claimed invention.

D) The disclosure does not provide an enabling description of a method having the steps of reacting B-cells with T-cells.

E) The disclosure does not provide an enabling description of fusion proteins of at least a portion of the extracellular domain of the CD28 receptor. The disclosure is specifically directed to a fusion containing amino acid residues, of the CD28 receptor, from about position 1 to 134 and a second amino acid sequence corresponding to the hinge, CH2 and CH3 regions of human IgG-1 constant domains.

F) Applicant's specification does not support a method of inhibiting T cell proliferation with any B7 antigen derivative. Specifically, B7 on CHO cells, or immobilized in any way will not result in a method of inhibiting. Instead, such a B7 derivative will cross-link the CD28 receptor resulting in T cell activation and increased proliferation. Additionally, the specification does not provide an enabling description of the use of an anti-CD2 antibody in a method of inhibiting T cell proliferation.

G) Applicant's specification does not support the scope of claims directed to a method for preventing the binding to the CD28 receptor to the B7 antigen. The specification discloses that a method of this type is use to inhibit functional T cell responses. However using a monoclonal antibody 9.3 to inhibit binding of B7 to CD28 will result in T cell activation and proliferation resulting in a functional T cell response.

H) It is unclear from the specification how the methods of claims 9, 10, 15, 17, 35 and 38 will result in inhibiting T cell proliferation. Note the deleted subject matter of claim 17, "T cell responses are stimulated". An anti-CD28 monoclonal antibody as that of claim 35 will cross-link the CD28 receptor resulting in activation of proliferation. This is why a Fab fragment such as that of claim 37 is necessary.

I) The specification does not enable a method of inhibiting proliferation using an intact antibody molecule to the CD28 receptor.

J) The specification does not contemplate the CTLA-4 molecule. Thus even if the CD28/B7 interaction is inhibiting the CTLA-4/B7 interaction can still activate T cells. Applicant is encouraged to consider Linsley et al. [J. Exp. Med. 174:561-569 (1991)].

26. Claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42 and 78 are rejected under 35 U.S.C. § 112, first paragraph, for the

reasons set forth in the objection to the specification.

27. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

28. Claim 37 is rejected under 35 U.S.C. § 102(b) as being anticipated by Ledbetter et al. [J.I. 135(4):2331-2335 (1985)]. Ledbetter et al. teach Fab fragments of anti-TP44(CD28) were ineffective in inducing T cell proliferation, see abstract. These antibody Fab fragments will inherently block the interaction between CD28 and B7. The Fab fragment is derived from monoclonal antibody 9.3.

29. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

30. Claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42 and 78 are directed to an invention not patentably distinct from claims 1-24 of commonly assigned 08/076,071.

> Applicant is required to either:
>
> (a) Name the first inventor of conflicting subject matter under 102(f) OR 102(g)

or;

(b) Show inventions were commonly owned.

31. Claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42 and 78 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of copending application Serial No. 08/076,071. Although the conflicting claims are not identical, they are not patentably distinct from each other because while one method may be used to "increase endogenous cellular production of ThCD28 lymphokine by a population of T cells" the factors involved are the same A person of ordinary skill in the art would find it prima facia obvious at the time the invention was made to inhibit the stimulatory ligand from interacting with the receptors on the cells in order to inhibit CD28 pathway activation.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

32. Claims 1, 3, 5-8, 18, 41 and 42 are rejected under 35 U.S.C. § 103 as being unpatentable over Linsley et al. [PNAS 87:5031-5035 (1990)] and Freeman et al. [J. Immunology 143:2714-1722 (1989)] in view of Capon et al. [WO 89/02922]. Briefly the claims are directed to a method of inhibiting T cell proliferation by blocking the interaction between the CD28 and B7 complex using the B7 antigen. Linsley et al. teach the interaction between CD28 and B7 is important in crosslinking CD28 and activating T cell proliferation, see entire paper. Linsley et al. do not teach a soluble B7 protein. Freeman et al. teach the sequence of the B7 molecule, figure 3, page 2717. Note that amino acid 217 begins the transmembrane portion of the molecule and amino acids 1-216 contain the extracellular portion of the molecule. Freeman et al. do not teach a B7Ig fusion. However, Capon et al. teach adhesion molecules fused to the constant domain of an immunoglobulin protein, see entire article. Capon teach that this stabilizes a solubilized receptor protein, increases plasma half life and improves therapeutic efficacy, see page 6, first full paragraph. The bridging paragraph of pages 9-10 teach functional domains of an adhesion protein is fused to the hinge, CH2 and CH3 domains of the constant region of an immunoglobulin heavy chain. Thus, from the combined teachings of Freeman et al. with Capon et al. a soluble B7Ig fusion protein would have been prima facia obvious to a person of ordinary skill in the art at the time the invention was made. Linsley et al. add to the combination of Freeman et al. and Capon et al. providing motivation to a person of ordinary skill in the art to inhibit the interaction between B7 and CD28 to inhibit the proliferation of T cells. Therefore as a whole the claimed invention is prima facia obvious to a person of ordinary skill in

the art at the time the invention was made.

33. Claims 19, 39, 40 and 78 are rejected under 35 U.S.C. § 103 as being unpatentable over Linsley et al. [PNAS 87:5031-5035 (1990)] and Aruffo et al. [PNAS 84:8573-8577 (1987)] in view of Capon et al. [WO 89/02922]. Briefly the claims are directed to a method of inhibiting T cell proliferation by blocking the interaction between the CD28 and B7 complex using the CD28 receptor. Briefly the claims are directed to a method of inhibiting T cell proliferation by blocking the interaction between the CD28 and B7 complex using the B7 antigen. Linsley et al. teach the interaction between CD28 and B7 is important in crosslinking CD28 and activating T cell proliferation, see entire paper. Linsley et al. do not teach a soluble B7 protein. Aruffo et al. teach the sequence of the CD28 molecule, figure 2, page 8574. Aruffo et al. do not teach a CD28Ig fusion. However, Capon et al. teach adhesion molecules fused to the constant domain of an immunoglobulin protein, see entire article. Capon teach that this stabilizes a solubilized receptor protein, increases plasma half life and improves therapeutic efficacy, see page 6, first full paragraph. The bridging paragraph of pages 9-10 teach functional domains of an adhesion protein is fused to the hinge, CH2 and CH3 domains of the constant region of an immunoglobulin heavy chain. Thus, from the combined teachings of Aruffo et al. with Capon et al. a soluble CD28Ig fusion protein would have been prima facia obvious to a person of ordinary skill in the art at the time the invention was made. Linsley et al. add to the combination of Aruffo et al. and Capon et al. providing motivation to a person of ordinary skill in the art to inhibit the interaction between B7 and CD28 to inhibit the proliferation of T cells. Therefore as a whole the claimed invention is prima facia obvious to a person of ordinary skill in the art at the time the invention was made.

34. No claims allowed.

35. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4227.

36. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donald E. Adams whose telephone number is (703) 308-0570. The examiner can normally be reached Monday through Thursday from 7:30 to 6:00. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. David Lacey can be reached on (703)

308-3535. The fax phone number for Group 180 is (703) 305-3014 or (703) 308-4227. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

August 8, 1994

Donald E. Adams, Ph.D.
Patent Examiner
Group 1800